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Formulations comprising praziquantel and
another anthelmintic

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Title: Formulations comprising praziquantel and another anthelmintic

DESCRIPTION

This invention relates to pharmaceutical compositions for the treatment of helminthiasis in warm-blooded animals, more particularly cattle, sheep, goats, and other domesticated herbivores.

BACKGROUND

Helminthiasis is a widely occurring disease in farmed animals. It commonly causes clinical disease and has significant adverse economic effects on farming economies when present at subclinical levels. Over the past twenty-five years a number of initially successful anthelmintic agents, with relatively specific effects on the metabolism of smaller or larger groups of endoparasites have been discovered, trialled, and used successfully to control helminthiasis on farms. Various groups of compounds have a greater or lesser spectrum of activity - that is to say they are able to destroy a wider or smaller range of parasite. For example, the widely used "ivermectin" is active against parasitic roundworms and also against some ectoparasites, yet it is inactive against tapeworms because of a difference in their biochemical constitution. "Triclabendazole" is active only against the liver fluke *Fasciola hepatica*.

Unfortunately, resistance to the effects of particular compounds or related families has usually developed with time, after repeated use of the same compound, and has become one of the major problems in the use of these arithelmintic agents. In fact, the growth of drench resistance seems to be overtaking the ability of scientists to develop new drenches. The spread of "sheep measles" (cysts of the *taenia ovis* species of tapeworm) is one such problem.

There is a need, therefore, for alternative anthelmintic formulations having the breadth of activity of the benzimidazole drugs (for example) but which slows the advancement of drench resistance.

OBJECT

It is an object of this invention to provide novel pharmaceutical compositions having anthelmintic activity.

According to the invention there is provided an anthelmintic composition including an effective amount of the anthelmintic praziquantel together with effective amounts of at least one other anthelmintic, wherein the other anthelmintic is selected from the group comprising the avermectins; milbemycins; levamisole; tetramisole; or a substituted benzimidazole carbamate, with the proviso that it does not include febantel, pyrantel, oxamniquine nor furapromidium.

Praziquantel (*2(Cyclohexylcarbonyl))-1,2,3,6,7,-11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one*) has for many years been used to control cestode infestations and schistosomiasis in humans. The surprising discovery that the efficacy of praziquantel can be enhanced in domesticated animals by simultaneous administration with other anthelmintics has been exploited in the present invention, which offers improved efficacy in the control of cestodes, together with simultaneous control of nematode infestations.

Examples of suitable benzimidazole drugs include drugs such as mebendazole, fenbendazole, oxfendazole, albendazole, cambendazole, parbendazole, oxibendazole, flubendazole and cyclobendazole.

Preferably, in the case of compositions incorporating levamisole, the composition has a pH less than 4.0 and in the most preferred aspect the pH is about 3.0.

Optionally, the composition may contain other veterinary products (including other anthelmintics).

The anthelmintic compositions of the invention may be used for treating helminthiasis in animals.

When administered to sheep we prefer to administer the composition as a drench having an effective amount of praziquantel in the range of 4 to 4 mg/kg of body weight.

Since praziquantel is a relatively insoluble material, we have devised formulations for administration in the form of drenches and examples are included in this specification.

We have previously found that combining benzimidazole drenches with levamisole drenches results in an unstable product due to the different pH values needed to maintain

the stability of the individual products. Mixtures of levamisole as the hydrochloride together with praziquantel are stable, provided that the pH of the mixture is lower than approximately 4.

These and other aspects of the invention, which will be considered in all its novel aspects, will be apparent from the following description, which is given by way of example only.

GENERAL FORMULATION

A typical formula for this invention would include the following active ingredients:

praziquantel	active in a range of activity from 0.5 - 15% w/v
AND	
benzimidazole	active in a range of activity from 1 - 15% w/v
OR	
levamisole	active in a range of activity from 1 - 10% w/v
OR	
ivermectin	active in a range of activity from 0.05 - 1% w/v
OR	
moxidectin	active in a range of activity from 0.05 - 1% w/v
OR	
doramectin	active in a range of activity from 0.05 - 1% w/v

and one or more of the following ingredients to enhance stability and characteristics of the composition:

viscosity agents
surfactants
sanitizers
acidifiers
stabilizers

EXAMPLE 1:Praziquantel/Levamisole HCl Drench

pH of 3.4

Density at 20 °C = 1.025 kg/l

Viscosity @ 20 °C

= 20 sec. (Ford no. 4 cup)

<i>Ingredient</i>	<i>gm/100ml</i>
Water (hot)	2.0
Polyoxystearate 40USP/NF	2.50
PEG 6000*	3.00
praziquantel	1.88
Defoamer RD	0.20
Water (cold)	to 100 ml
Potassium sorbate BP	0.18
Citric Acid (anhyd) BP	0.30
Levamisole HCl BP	3.75
Xanthan Gum USP/NF	0.20
Mono propylene glycol BP	0.40
Colloidal anhydrous silica BP	1.00
Formaldehyde solution BP	0.20
	100.00

*PEG 6000 is an abbreviation for Polyethylene Glycol 6000 USP/NF.

We have found that it is possible to make an acidified praziquantel drench in which the stability of levamisole can be maintained without affecting the praziquantel component. The acidity of the resulting product is preferably of a pH of less than 4.0, preferably around 3.0. A lower pH down to 2.0 is preferable if minerals are added to the drench. We have found that the pH of the above examples will vary slightly on a batch by batch basis.

Manufacturing Instructions for Composition of Example 1

1. Praziquantel premix - measure the hot water into a premix vessel, add the PEG 6000 and polyoxystearate 40 and mix until fully melted (approximately 65°C). Use external heating if required. Add the praziquantel and Defoamer RD and silverson until smooth and lump free.
2. Measure the bulk of the cold water into the production tank, add the potassium sorbate, citric acid, and levamisole hydrochloride and stir to dissolve.
3. Add the hot praziquantel premix to the production tank and stir until fully dispersed and lump-free.
4. Premix the Monopropylene glycol and Xanthan Gum, add to the batch and silverson until dispersed and until the viscosity has fully developed.
5. Add the colloidal anhydrous silica and silverson until fully dispersed.
6. When the batch temperature is below 40°C add the formalin and stir to dissolve.
7. Add the remaining water to make up to volume.
8. Take a test sample for laboratory analysis.

The procedure called "silversoning" is essentially mixing or dispersing in a device providing high shear rates within the fluid.

EXAMPLE 2:Praziquantel/Albendazole Drench

By way of a second embodiment, a combination with an albendazole would be prepared using the following constituents:

	<i>gm/100ml</i>
Water (hot)	2.00
PEG 6000	2.50
Polyoxystearate 40	3.00
Albendazole	2.38
Defoamer RD	0.20
Praziquantel	2.50
Water (cold) to 100ml	
Potassium sorbate	0.18
Citric acid	0.30
Xanthan Gum USP/NF	0.20
Monopropylene glycol	0.40
Formalin	0.20
Colloidal anhydrous silica	1.00
	100 ml

The pH of such a suspension is expected to be in the range of from 3.5 to 5.5.

Combinations with other benzimidazole-type compounds can be formulated in a manner similar to that of Example 2.

EXAMPLE 3:Praziquantel/Ivermectin Drench

Combinations with avermectin-related compounds can be made as non-aqueous or aqueous suspensions depending on the stability of the avermectin compound. For example, a formulation including ivermectin and praziquantel could be:

	<i>gm/100ml</i>
Ivermectin	0.1
Praziquantel	1.88
Propylene glycol	40.00
Water	to 100ml

The suspension would have a neutral pH.

Other avermectins such as doramectin or moxidectin may be used in place of ivermectin.

It is also possible to prepare a solution of praziquantel with appropriate organic solvents.

The resulting product is not only stable but also allows the farmer to obtain control of a wider range of parasites.

EXAMPLE 4:Praziquantel/Oxfendazole

A combination with an albendazole would be prepared using the following constituents:

	<i>gm/100ml</i>
Water (hot)	2.00
PEG 6000	2.50
Polyoxystearate 40	3.00
Oxfendazole	2.265
Defoamer RD	0.20
Praziquantel	2.50

Water (cold) to 100ml	
Potassium sorbate	0.18
Citric acid	0.30
Xanthan Gum USP/NF	0.20
Monopropylene glycol	0.40
Formalin	0.20
Colloidal anhydrous silica	1.00

	100 ml

EXAMPLE 5:Praziquantel/Moxidectin

	gm/100ml
Praziquantel	2.0
Moxidectin	0.10
Propylene glycol	20.0
Xanthan Gum USP/NF	0.2
Water	to 100 ml

	100ml

EXAMPLE 6:Praziquantel/Ivermectin

	gm/100ml
Praziquantel	2.0
Ivermectin	0.08
Ethanol	20.0
Propylene glycol	to 100ml

	100 ml

In addition, it is possible to include in the composition other veterinary products including ectoparasiticides, as well as other endoparasiticides, minerals, and trace elements as required. In the following trials reference will be made to the praziquantel/levamisole formulation of Example 1. In some of the trials the formulation of Example 1 may include minerals and trace elements.

The compositions may be administered to mammals preferably by mouth as a drench, and as a single dose.

TRIALS

The formulation of Example 1 has been shown in a series of New Zealand trials to be highly effective in controlling benzimidazole resistant roundworms and tapeworms in sheep.

While levamisole has been well researched for the control of helminths in sheep, there historically has been little information on praziquantel in the ovine. Thomas & Gonnert [Research in Veterinary Science (1978) 24,20] report a high efficacy in the control of *Moniezia* spp at a dose of 2.5mg/kg, while other studies against liver tapeworm (*Stilesia hepatica*) demonstrated efficacy at 15mg/kg.

A recent study by C. Bauer [Veterinary Record (1990) 127, 353-354] demonstrated an adequate efficacy against *Moniezia expensa* in lambs at a dose of 3.75mg/kg. Based on this study a praziquantel dose of 3.75mg/kg was chosen.

TRIAL ISummary

Two groups of milk lambs - slaughter at ten days. The formulation of Example 1 at a dose of 2ml/10kg of body weight.

epg Reduction %	Formulation of Example 1	Control
Strong	98%	(800%)
Nem.		
% Reduction worm counts versus controls		
	Haemonchus spp	100%
	Ostertagia spp	97%
	Nematodirus spp	100%
	Trichostrongylus spp	100%
	Cooperia	100%
	Moniezia	
	Scoleces	100%
	Segments	98%

A high level of efficacy was demonstrated by the formulation of Example 1 against roundworms and tapeworms.

TRIAL REPORT I**OBJECTIVE**

To assess by dosing and slaughter trial the efficacy and dose compatibility of the formulation of Example 1 on lambs in the control of tapeworm and roundworm.

MATERIALS

The formulation of Example 1

TRIAL DESIGN

Two groups of lambs were divided into two random groups as follows:

Group 1

Dosed with the formulation of Example 1

Dose rate 2 ml/10kg bodyweight

Lambe Nos. 43, 42, 55, 23, 14, 61, 45, 47

All lambs were tagged, weighed and faecal sampled predosing.

All lambs were slaughtered at 10 days post treatment and tapeworm and nematode worm counts done on the abomasum and small intestine.

Reaction of animals at drenching observed and no effects noticed

Tag No.	Wgt kgs	Dose ml	EGGS/GRAM		10 DAY CRITICAL SLAUGHTER WORM COUNTS							MONIEZIA Scolex Segments mL
			Strong.	Nem.	Strong.	Nem.	Haem.	Ostert.	Trich.	Nema.	Trich.	
GROUP 1 - LEVITAPE 4ml/10kg												
43	22	8.8	250	-	-	-	-	500	-	-	-	-
42	24	9.6	50	-	-	-	-	-	-	-	-	-
55	20	8.0	350	-	-	-	-	200	-	-	-	-
23	15	6.0	650	-	-	-	-	-	-	-	-	-
14	16	6.4	2200	-	-	-	-	400	-	-	-	-
61	17	6.8	300	-	-	-	-	-	-	-	-	-
45	22	8.8	250	-	-	-	-	-	-	-	-	5
47	19	7.6	200	-	50	-	-	-	-	-	-	-
MEAN			531.2	-	6.2	-	-	137.5	-	-	-	0.6
GROUP 2 - CONTROL												
37	20	-	1650	-	3750	-	150	14000	-	200	2200	400 8 3
20	16	-	1000	-	2800	-	250	1400	-	-	1000	200 8 100
5	-26	-	900	-	1400	-	40	6000	-	-	2600	400 3 1
11	19	-	600	-	950	-	180	800	-	-	600	200 - -
17	20	-	600	-	2650	-	70	3000	-	100	700	500 2 8
63	17	-	400	-	2400	-	140	5800	-	100	2000	800 2 45
51	18	-	100	-	950	-	10	1600	-	100	600	100 2 60
32	18	-	200	-	450	-	30	2400	-	-	500	200 2 35
MEAN			681.2	-	6168.7	-	878	4375	-	62.5	1275	350 3.3 31.5

The tabulated results above show for each result the weights of the lambs, the dose administered, the faecal egg counts predosing and the 10 day worm counts. The efficacy of the formulation of Example 1 on *Moniezia expansa* is demonstrated. The levamisole shows no diminution in its efficacy on the common nematodes in lambs.

TRIAL II

Summary

Three groups of lambs - slaughter at ten days.

Group 1 Formulation of Example 1 - 1ml/5kg

Group 2 Albendazole - 1ml/5kg

Group 3 Control - untreated

% epg Reduction	Formulation of Example 1	Albendazole	Control
Strong	15%	45%	(788%)
Nem	100%	+	+
% Reduction	Haemonchus spp	60%	30%
worm counts	Ostertagia spp	82%	96%
versus	Nematodirus spp	85%	(23%)
controls	Trichostrongylus spp	100%	25%
	Cooperia spp	-	-
	Moniezia		
	Scoleces	99%	19%
	Segments	100%	23%

Clear evidence of resistant nematodes to levamisole and albendazole.

Albendazole resistant moniezia were cleared by the formulation of Example 1.

TRIAL REPORT II**OBJECTIVE**

To assess by dosing and slaughter trial the efficacy and dose compatibility of the formulation of Example 1 on lambs in the control of tapeworm and roundworm.

MATERIALS

1. Formulation of Example 1
8mg/kg levamisole/3.75 mg/kg praziquantal
2. Albendazole

TRIAL DESIGN

Three groups of lambs were divided into three random groups as follows:

Group 1 - 8 Lambs, Group 2 - 8 Lambs, Group 3 - 7 Lambs.

Group 1 Dosed with the formulation of Example 1
(3.75 mg/kg praziquantal)
(8mg/kg levamisole)

Dose rate 1 ml/1 kg bodyweight
Lamb Nos. 50, 54, 37, 75, 35, 35, 30, 61, 52

Group 2 Albendazole 1ml/5kg
Lamb Nos. 48, 64, 56, 33, 60, 58, 44, 59

Group 3 Control
Lamb Nos. 40, 32, 57, 49, 43, 46, 51

All lambs were tagged, weighed and faecal sampled predosing.

All lambs were slaughtered at 10 days post treatment and tapeworm and nematode worm counts done on the abomasum and small intestine.

Reaction of animals at drenching observed and no effects noticed.

Tag No.	Wgt. kgs	Dose ml	EGGS/GRAM		10 DAY CRITICAL SLAUGHTER WORM COUNTS									
			Strong.	Nem.	Strong.	Nem.	Haem.	Oster.	Trich.	Nema.	Trich.	Coop.	MONIEZIA	Sclex
GROUP 1 - LEVITAPE II (1ml/5kg)														
50	16	3.0	1900	100	-	-	-	100	-	100	-	-	-	-
54	14	3.0	50	-	-	-	-	-	-	30	-	-	-	-
37	14	3.0	450	-	-	-	-	-	-	-	-	-	-	-
75	13	3.0	600	-	-	-	-	10	-	-	-	-	-	-
35	14	3.0	350	50	750	-	-	200	-	100	-	-	1	-
30	14	3.0	900	-	2850	-	100	1900	-	-	-	-	-	-
61	12	2.5	300	-	-	-	-	20	-	-	-	-	-	-
52	26	5.0	300	-	-	-	Missing							
MEAN			606.3	18.8	514	-	14.3	318.6	-	32.8	-	-	0.14	-
GROUP 2 - ALBENDAZOLE (1ml/5kg)														
48	16	-	750	-	50	-	30	100	-	100	-	-	55	-
64	14	-	-	-	500	-	30	100	-	20	-	-	4	-
56	14	-	450	-	150	-	-	-	-	700	-	-	11	40
33	13	-	150	-	400	-	20	-	-	1000	100	-	34	10
60	14	-	2250	-	1000	200	40	100	-	100	-	-	39	27
58	14	-	900	-	700	50	20	-	100	100	-	-	16	14
44	12	-	700	-	150	50	100	200	-	100	-	-	29	3
59	26	-	950	-	400	-	-	-	-	10	-	-	4	-
MEAN			768.7	-	418.8	37.5	30.0	62.5	12.5	266.3	112.5	-	24.0	11.8
GROUP 3 - CONTROL														
40		450	-	1350	-	40	1200	-	300	100	-	24	15	
32		850	-	7300	500	60	2500	-	400	200	-	3	-	
57		500	-	950	50	30	1000	-	300	-	-	18	1	
49		-	-	1750	150	20	400	-	-	-	-	52	45	
43		750	-	1050	-	30	3200	-	200	100	-	49	30	
46		450	-	13450	-	40	2200	-	100	500	-	32	2	
51		400 DEAD												
MEAN			485.7		4308.0	116.0	36.6	1750	-	216.6	150.0	-	29.6	15.5

The tabulated results above show for each result the weights of the lambs, the dose administered, the faecal egg counts predosing and post dosing and the 10 day worm counts. The efficacy of the formulation of Example 1 on Moniezia expansa is demonstrated. The levamisole and albendazole group results shows efficacy on the common nematodes in lambs is not as high as desired as resistance appears to be present to both these actives.

The albendazole was not effective in its efficacy against Monezia expansa. The formulation of Example 1 shows a very successful level of elimination of this tapeworm when in combination with levamisole.

TRIAL REPORT III

LOCATION

OBJECTIVE

To assess by dosing and slaughter trial the efficacy and dose compatibility of the formulation of Example 1 on lambs in the control of tapeworm and roundworm.

MATERIALS

1. The formulation of Example 1 including minerals and trace elements such as copper, cobalt, selenium, iodine and zinc.
8mg/kg levamisole/3.75 mg/kg praziquantal
with Minerals
2. Albendazole (Valbazen)

TRIAL DESIGN

Three groups of lambs were divided into three random groups as follows:

Group 1 - 8 Lambs, Group 2 - 8 Lambs, Group 3 - 8 Lambs

Group 1

Dosed with the formulation of Example 1 including minerals and trace elements such as copper, cobalt, selenium, iodine and zinc.
(3.75 mg/kg praziquantal)
(8mg/kg levamisole)

Dose rate 1 ml/5 kg bodyweight

Lamb Nos. 17, 20, 23, 33, 36, 37, 102, 108

Group 2 Albendazole 1ml/5kg

Lamb Nos. 12, 21, 26, 39, 43, 46, 51, 103

Group 3 Control

Lamb Nos. 10, 11, 18, 32, 41, 49, 105, 109

All lambs were tagged, weighed and faecal sampled predosing. All lambs were slaughtered at 9 days post treatment and tapeworm and nematode worm counts done on the abomasum and small intestine.

Reaction of animals at drenching observed and no effects notice.

GROUP 2 - ALBENDAZOLE (1ml/5kg)

12	26	5.0	50	-	5	-	160	-	-	-	-	-	3	10
21	22	4.5	-	-	-	-	10	-	-	-	-	-	5	-
26	28	5.5	100	-	-	-	50	-	-	-	-	-	-	-
39	24	5.0	100	-	-	-	20	-	-	-	-	-	1	-
43	26	5.0	150	-	50	-	-	-	-	-	-	-	1	5
46	30	6.0	-	-	50	-	-	-	-	-	-	-	35	-
51	28	5.5	100	-	-	-	-	-	-	-	-	-	5	-
103	20	4.0	300	-	-	-	450	-	-	-	-	-	-	-
MEAN		100.0	-	13.1	-	86.3	-	-	-	-	-	-	6.9	11.8

GROUP 3 - CONTROL

10	22	100	-	600	-	650	100	-	-	700	200	6	110
11	24	250	-	2250	-	1400	400	-	-	2200	4000	2	85
18	22	-	-	400	-	880	300	-	100	1800	3200	2	80
32	30	50	-	-	-	400	600	-	100	200	300	8	15
41	26	100	-	50	-	50	100	-	-	200	-	-	-
49	22	50	-	950	-	560	200	-	100	-	-	-	-
105	24	150	-	1400	-	700	100	-	-	1600	4800	2	55
109	26	-	-	1150	-	970	200	-	-	800	1400	-	40
MEAN		87.5	-	850	-	701.3	250	-	37.5	937.5	1738	2.5	48.1

The tabulated results above show for each result the weights of the lambs, the dose administered, the faecal egg counts predosing and post dosing and the 9 day worm counts. The efficacy of the formulation of Example 1 including minerals and trace elements on *Moniezia expansa* is demonstrated. The albendazole group results shows efficacy on the common nematodes in lambs is not as high as desired as resistance appears to be present to this active for *Haemonchus contortus*.

The albendazole was not effective in its efficacy against *Monezia expansa*. The formulation of Example 1 shows a very successful level of elimination of this tapeworm when in combination with levamisole, with no diminution in efficacy by levamisole against the common nematodes in lambs.

VARIATIONS

A range of compositions have been described suitable for the treatment or prevention of helminthiasis in sheep and goats. The trials show dose rates of 3.75 mg/kg of praziquantel and 8mg/kg of levamisole. We have discovered that the dose rate of the formulation of Example 1 can be reduced, thereby reducing the dose rate of praziquantel to about 2mg/kg whilst preventing sheep measles in lambs. Preferred dose rates for lambs and sheep are in the range of 2-7.5 mg/kg of live body weight of praziquantel, giving a comparable range of levamisole of 4-16 mg/kg of live body weight.

Any of the avermectins, ivermectin, moxidectin, doramectin, could be replaced by Milbemycin D or other members of the Milbemycin family (Merck Index 6112, 11th Edition).

Finally it will be appreciated that various other alterations and modifications may be made to the foregoing without departing from the scope of this invention as set forth in the following claims.

CLAIMS

1. An anthelmintic composition including an effective amount of the anthelmintic praziquantel together with effective amounts of at least one other anthelmintic, wherein the other anthelmintic is selected from the group comprising the avermectins; milbemycins; levamisole; tetramisole; or a substituted benzimidazole carbamate, with the proviso that it does not include febantel, pyrantel, oxamniquine nor furapromidium.
5. 2. An anthelmintic composition as claimed in claim 1, wherein the composition includes levamisole, and the composition has a pH of less than 4.0.
10. 3. An anthelmintic composition as claimed in claim 2, wherein the pH is about 3.0.
15. 4. An anthelmintic composition as claimed in claim 1, wherein the formulation is a drench and contains from 0.5 to 15% w/v of praziquantel.
20. 5. An anthelmintic composition as claimed in claim 4, wherein the formulation contains levamisole hydrochloride from 1 to 10% w/v.
6. An anthelmintic composition as claimed in claim 4, wherein the formulation contains from 0.05 to 1% w/v of ivermectin or moxidectin or doramectin.
25. 7. An anthelmintic composition as claimed in claim 4, wherein the formulation contains from 1-15% w/v of a

benzimidazole chosen from the group comprising mebendazole, fenbendazole, oxfendazole, albendazole, cambendazole, parbendazole, oxibendazole, flubendazole and cyclobendazole.

5 8. An anthelmintic composition as claimed in any one of claims 1 to 7, wherein the praziquantel is suspended in a liquid carrier.

9. An anthelmintic composition substantially as herein described with reference to any one of the
10 Examples.